



7-18-86 RF

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 18 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Response (5/15/86) by Shell Development Co. to the data gaps identified in the Residue Chemistry Chapter of the 9/85 Monocrotophos Registration Standard (RCB #'s 1002, 1003, 1004, 1005, 1006, 1007). Accession No. 262893

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THRU: Charles L. Trichilo, Ph.D., Chief
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TO: Amy Rispin, Chief
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and

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Background

In response to the data gaps cited in the Monocrotophos Registration Standard (9/85), Shell has submitted a goat metabolism protocol for RCB's review, a request for a waiver of the poultry metabolism study, and a letter summarizing Shell's intentions regarding plant and animal metabolism studies and ruminant feeding studies. Shell's submission of 1/14/86 (see review of 5/21/86) briefly addressed some of these deficiencies. Pertinent data gaps cited in the Registration Standard will be restated below, followed by Shell's response and RCB's Comments/ Conclusions.

Note to PM: In compliance with the Dr. C.L. Trichilo (Chief-RCB) memo of 6/14/86, RCB is returning the TOX and Domestic Animal Safety sections of this submission to the RD/PM.

§ 158.125 Residue Chemistry

171-2: Chemical Identity: The same chemical identity data as required under § 158.120 are required, with emphasis on impurities that would constitute a residue problem.

Shell's Response

Shell intends to provide the data; no submission date was given.

RCB's Comments/Conclusions

The data have not yet been submitted. RCB notes that the due date for data gap 171-2 is March, 1986. This data gap is still outstanding. The Registrant should be reminded that his submission is overdue (see RCB's review of 5/21/86).

171-3: Directions for Use: Required information includes crops to be treated, rate of application, number and timing of applications, preharvest intervals, and relevant restrictions.

Shell's Response

Shell intends to provide the data; no submission date was given.

RCB's Comments/Conclusions

The data have not yet been submitted. RCB notes that the due date for data gap 171-3 is March, 1986. This data gap is still outstanding. The Registrant should be reminded that his submission is overdue (see RCB's review of 5/21/86).

171-4: Nature of the Residue (Metabolism)

Plants

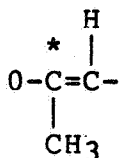
The following additional data are required:

- ° Residues of [³²P] or [¹⁴C] monocrotophos must be characterized and quantified in or on cottonseed produced from seed treated with 25 lb a.i./ton of delinted seed. Exaggerated rates may be necessary to obtain sufficient activity for identification
- ° Residues of [³²P] or [¹⁴C] monocrotophos must be characterized and quantified in or on peanuts grown in

soil treated twice at 1 lb a.i./A; peanuts must be harvested 15 days after the final application. Exaggerated rates may be necessary to obtain sufficient activity for characterization. The residue data must also include residues for the trimethyl phosphate contaminant.

- ° In addition the Office of the Assistant Administrator has requested that the residue data show evidence regarding the fate and stability of trimethyl phosphate (TMP) in plants.
- ° Crop field trials should not be started until the plant metabolism study has been completed.

NOTE: Labeling should take place at carbon atom with asterisk:



Shell's Response re: Cotton Metabolism

Shell stated in its submission of 1/14/86 that it does not intend to support the cottonseed treatment but that a cotton plant study would be carried out with radiolabeled Azodrin to support foliar application to cotton.

In this submission, Shell has submitted a protocol of the cotton plant study for RCB's review. The purposes of the study are:

1. To determine the nature and magnitude of the residue in cottonseed following an application rate of 3 x 1 lb. a.i./A.
2. To provide ^{14}C -labeled, treated cotton plant tissue to determine the extraction efficiency of the current enforcement method and storage stability.
3. To provide treated cotton plant tissue for the measurement of residues of trimethyl phosphate.

In this greenhouse study, cotton plants will be treated with ^{14}C -monocrotophos at a rate equivalent to 1 lb. a.i. per acre. The Azodrin will be labeled as specified in the Monocrotophos Registration Standard and will be fortified with 1% TMP.

For determining the extraction efficiency, plants will receive one foliar application of Azodrin possessing a specific activity of 1 microCurie/mg. For residue analysis in cottonseed, plants will be sprayed three times with Azodrin possessing a specific activity of 5 microCuries/mg. The limit of detection is claimed to be 0.05 ppm. Foliar application will be made before any bolls are open, when the first bolls open, and 10 days after the first bolls open.

Only cottonseed and lint are to be analyzed. According to the protocol, "Samples will be harvested immediately after treatment for storage stability, extraction efficiency, and TMP analysis." In order to investigate the nature and magnitude of the residue in cottonseed, samples will be harvested after maturity following 3 applications. Foliage residue will not be analyzed in this abbreviated study because, according to the Registration Standard, the nature of the residue following foliar application is adequately understood.

Shell intends to seek a waiver of the ruminant feeding study and processed commodity study, if there are no detectable residues in plants or cottonseed.

RCB's Comments/Conclusions

The registrant states, "Samples will be harvested immediately after treatment for storage stability, extraction efficiency, and TMP analysis." Apparently freshly treated samples will be used to investigate the extraction efficiency. This study could be more informative if weathered residues were used to determine the extraction efficiency. Furthermore, this study could provide complete validation of the analytical methodology (instead of merely the extraction efficiency as indicated above by the registrant) if the extracts were to be subjected to the determinative step of the enforcement method (GLC with an FPD or NPD). Therefore, RCB suggests that weathered residues be used to validate the enforcement methodology.

Since the stability of monocrotophos under freezer conditions is open to question, the proposed study could delineate the degradative processes which appear to occur during storage. However, no specifics of the storage stability study were provided with this submission. RCB suggests that Shell provide more details of the proposed storage stability study.

Since the Office of the Assistant Administrator has requested information on the metabolism and persistence of TMP (trimethyl phosphate), which may be an impurity of the technical material, this issue will need to be addressed either in the cotton plant study or the peanut study, which is discussed below. Therefore, radiolabeled TMP should be used. RCB agrees with

the registrant that the cotton study is better suited to determine the fate of TMP residues, because a foliar application is proposed for use in this study, whereas the peanut study will employ a soil application. The metabolism of TMP following a foliar application is not adequately understood. The registrant may want to use both ^{32}P and ^{14}C in his studies.

The registrant intends to seek a waiver from the requirement of a ruminant feeding study if no detectable radioactive residues are found in cotton plants or cottonseed. However, according to the submitted protocol, the registrant intends to analyze only the cottonseed and lint. Cotton forage and gin trash may be fed to livestock. In any case, the available residue data indicate that levels of Azodrin can be expected to range up to 2 ppm in corn forage. Therefore, RCB would not consider it appropriate to waive the requirement for a ruminant feeding study, solely on the basis of undetectable residues on cottonseed and lint.

In its 1/14/86 submission, Shell had agreed to provide residue data from a cottonseed processing study. However, Shell now intends to seek a waiver from the cottonseed processing study, if the cotton plant studies show that there are no detectable residues of activity in the plant or in cottonseeds. In the past, RCB has concluded that processing studies are not needed, if there are no detectable residues of a pesticide following application at greatly exaggerated rates (ca 10 X). The application rate in the study described above is not an exaggerated rate. Therefore, RCB recommends that the requirement for a cottonseed processing study not be waived. The processing study should utilize crops treated at exaggerated rates.

Shell's Response re: Peanut Metabolism

In the present submission, Shell reaffirms its intention (first stated in its 1/14/86 submission) to conduct a peanut metabolism study which will reflect soil application only. Shell intends to amend the label for use of Azodrin on peanuts. One band application will be permitted no later than 45 days before harvest. Azodrin is currently registered for use on peanuts at a rate of 1 lb. a.i./A; band and foliar applications are permitted. Two applications per season are permitted; a 15 day PHI is imposed.

Shell submitted an outline of the protocol of the peanut metabolism study for RCB's review.

^{14}C -Monocrotophos, labeled as specified in the Registration Standard, will be applied to the soil 45 days before harvest; an application rate of 1 lb. per acre will be used. The peanuts will be grown outdoors. The specific activity of the monocrotophos

will be about 5 microCuries/mg; the limit of detection would then be 0.05 ppm. Green tissue (leaves and stems), peanut hulls, and nutmeats will be analyzed.

If there are no detectable residues in the plant or peanuts, the registrant intends to request a waiver of the ruminant feeding study.

RCB's Comments/Conclusions

The outline of the protocol was not very detailed; the registrant needs to specify the following:

1. RCB needs to know how the radiochemical will be applied to the soil and whether the application rate (given as 1 lb/A) is actually 1 lb a.i./A;
2. The registrant will need to specify the kind of soil that will be used in this study;
3. The registrant needs to specify the storage conditions. RCB suggests that analysis be undertaken as soon as is feasible because there may be problems with storage stability;
4. The registrant needs to describe the proposed methods of analysis (TLC, HPLC, GC-MS, etc.), as he did in the crop rotation protocol. The registrant intends to "monitor" uptake of radioactive soil residues by peanuts; however, Shell will also need to identify these residues if significant uptake occurs; and
5. Since the study will be done outdoors, the registrant should also keep a record of the rainfall and other climatic conditions.

The Office of the Assistant Administrator has requested information on the metabolism and persistence of TMP. Therefore, this issue will need to be addressed.

The proposed tolerances for residues of monocrotophos on corn forage and grain are 2.0 and 0.3 ppm, respectively. Therefore, RCB would not consider it appropriate to waive the ruminant feeding study solely on the basis of undetectable residues of monocrotophos in/on peanut plants, nutmeats, and hulls.

Since the plant metabolism data have not yet been submitted, data gap 171-4, plant metabolism, is still outstanding.

171-4 Nature of the Residue (Metabolism)

Livestock

The following additional data are required:

- ° Metabolism studies utilizing ruminants. Animals must be dosed for 3 days with either [³²P] or [¹⁴C] monocrotophos at a concentration in the total diet which will result in sufficient residues in the milk, liver, muscle and fat for characterization. Animals must be sacrificed within 24 hours of the final dose (milk must be collected twice daily).
- ° Metabolism studies utilizing poultry. Animals must be dosed 3 days with either [³²P] or [¹⁴C] monocrotophos at a concentration in the total diet which will result in sufficient residues in the eggs, liver, kidney, fat, and muscle for characterization. Eggs must be sampled twice daily throughout the treatment period. Animals must be sacrificed within 24 hours of the final dose. If poultry metabolism is found to differ significantly from that of ruminants, then nonruminant (swine) data will be required (i.e., in the absence of rat metabolism data). If poultry and ruminant metabolism differ from that in the rat, then additional swine data are required. (Note: the type of labeling should be the same for both animal and plant metabolism studies.)

Shell's Response re: Ruminant Metabolism

Shell will conduct a lactating goat metabolism with ¹⁴C-Azodrin. If negligible levels of radioactivity are detected in milk and tissue, Shell contends that a ruminant feeding study is not needed.

An outline of the protocol was submitted for RCB's review.

¹⁴C-Monocrotophos, labeled as specified in the Registration Standard, will be fed by capsule to 2 female goats weighing about 40 kg. A dose equivalent to about 10 ppm in the feed will be fed to the goats for 3 days. The registrant states that this dosage represents 10 times the dietary burden imposed upon a dairy cow consuming a diet composed of 50% corn forage (proposed tolerance, 2.0 ppm). A third goat will be maintained as a control.

The specific activity of the monocrotophos will be 36 microCuries per mg. The registrant states that the limit of detection by radioassay would be 0.01 ppm total ¹⁴C-residues (50 mg tissue or milk per analysis). The detection limit for metabolite

characterization would be ≥ 0.05 ppm.

The animals will be slaughtered 24 hours after the last dosing. Urine and feces will be collected daily; milk will be collected twice daily. Monitoring for ^{14}C is not scheduled. Samples of liver, muscle, fat, and kidney will be collected. Milk will be separated into milk fat and skim milk. The petitioner intends to effect "total ^{14}C -characterization" in milk and tissue.

RCB's Comments/Conclusions

The registrant has presented the protocol in a tabular form, which is very condensed. RCB has the following questions:

1. How does the registrant plan to store his samples before radioanalysis? Since there have been storage stability problems with monocrotophos, RCB suggests that storage time be kept to a minimum.
2. How does the registrant intend to characterize the radioactive residues?

RCB suggests that if rigorous acidic or basic conditions are used during the course of metabolic characterization, the registrant should determine the stability of Azodrin under those conditions; according to the EAB Chapter of the Registration Standard, Azodrin decomposes slowly at pH's 3-9 at 25-35°C.

At this time RCB can draw no conclusions on the feasibility of waiving the requirement for a ruminant feeding study.

The data gap regarding ruminant metabolism remains outstanding.

Shell's Response re: Poultry Metabolism

Shell requests that the requirement for the poultry metabolism study be waived for the following reasons:

1. The residue levels of monocrotophos in cotton, sugar cane, and peanut are negligible; and
2. Commodities derived from the above crops constitute a small fraction of poultry feed (i.e., cottonseed-3%, cotton soapstock-10%, peanut meal-10%, peanut soapstock, 5%, sugar cane molasses-4%).

Shell contends that under 40 CFR 180.6 (a)(3), a poultry metabolism study is not needed.

RCB's Comments/Conclusions

The petitioner has neglected the dietary burden which could be imposed upon poultry by the proposed tolerance on corn grain, 0.3 ppm. Corn grain may comprise up to 70% of the diet of a laying hen; therefore, the dietary burden imposed by corn grain is about 0.2 ppm. RCB can't estimate the dietary burden imposed upon poultry by soapstock and molasses because it is not yet known whether residues of Azodrin will concentrate in these commodities.

According to 40 CFR 180.6 (a)(3), "When it is not possible to determine with certainty whether finite residues will be incurred in milk, eggs, meat, and/or poultry but there is no reasonable expectation of finite residues in light of data such as those reflecting exaggerated pesticide levels in feeding studies and those elucidating the biochemistry of the pesticide chemical in the animal, a tolerance may be established on the raw agricultural commodity without the necessity of a tolerance on food products derived from the animal."

In other words, the decision on the need for poultry and egg tolerances is made on the basis of feeding studies and metabolism studies. The decision should not be made in the absence of such studies. RCB recommends that the poultry metabolism study not be waived.

The data gap regarding poultry metabolism remains outstanding.

Other Comments

In addition to resolving the data gaps outlined above (171-2: Chemical Identity, 171-3: Directions for Use, and 171-4: Nature of the Residue-plants, livestock and poultry), the registrant will also need to resolve the following data gaps that are discussed in RCB's 5/21/86 review of the registrant's response of 1/14/86:

- 171-4: Storage Stability (Peanuts)
- 171-4: Magnitude of the Residue-residue studies for each food use
- 171-5: Reduction of Residue
- 171-6: Proposed Tolerance
- 171-7: Reasonable Grounds in Support of Petition
- 171-11: Tobacco

cc: A. Barton,, Monocrotophos Reg. Std. File-W. Boodee, PMSD/ISB,
R.F., Reviewer-Deyrup, W. Miller-PM #16, Circu., Monocrotophos
Subject File

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TS-769:RCB:CM#2:RM810:X7484:CDeyrup:cd:7/16/86